Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1657	sphere same membrane	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:29
L2	1	l1 an coated same polymer	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:31
L3	159	l1 and hydrophobic same polymer	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:32
L4	134	l3 and hydrophilic	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:32
L5	18	l4 and sphere same coating	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:37
L6	19	l1 and support and pvdf	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:37
L7	10	l6 and pva	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:52
L8	453	coated particles and l1	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:52
L9	112	l8 and spherical same particles	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:53
L10	0	l9 and pvdf same hydrophilic	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:53
L11	0	l9 and hydrophiolic same hydrophobic	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:54
L12	20	l9 and polymer same hydrophobic and hydrophilic	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:55
L13	0	membrae same shape same spher?	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:56
L14	29	l1 and shape same spherical same support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:57
L15	8097	spherical support and membrane	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:58

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L16	0	l15 and caoting same support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:58
L17	270	l15 and coat same support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:58
L18	10	l17 and polymer and pvdf	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:02
L19	369	210/500.42	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:02
L20	0	l9 and suppor and sphere	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:03
L21	0	sapherical support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:03
L22	87168	spherical support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:03
L23	8097	l22 and membrane	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:04
L24	2373	l23 and composite	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:04
L25	162	l24 and layer same sphere	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:04
L26	29	l19 and l24	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:05

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1657	sphere same membrane	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:29
L2	1	l1 an coated same polymer	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:31
L3	159	l1 and hydrophobic same polymer	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:32
L4	134	l3 and hydrophilic	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:32
L5	18	l4 and sphere same coating	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:37
L6	19	l1 and support and pvdf	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:37
L7	10	l6 and pva	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:52
L8	453	coated particles and l1	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:52
L9	112	l8 and spherical same particles	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:53
L10	0	l9 and pvdf same hydrophilic	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:53
L11	0	l9 and hydrophiolic same hydrophobic	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:54
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L13	0	membrae same shape same spher?	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:56
L14	29	l1 and shape same spherical same support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:57
L15	8097	spherical support and membrane	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:58

L16	0	l15 and caoting same support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:58
L17	270	l15 and coat same support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 21:58
L18	10	l17 and polymer and pvdf	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:02
L19	369	210/500.42	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:02
L20	0	l9 and suppor and sphere	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:03
L21	0	sapherical support	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:03
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L23	8097	l22 and membrane	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:04
L24	2373	l23 and composite	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:04
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L26	29	l19 and l24	USPAT; EPO; DERWENT	AND	ON	2005/09/27 22:05

US-PAT-NO: 5683916

DOCUMENT-IDENTIFIER: US 5683916 A
See image for Certificate of Correction

TITLE: Membrane affinity apparatus and purification methods related thereto

DATE-ISSUED: November 4, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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APPL-NO: 08/ 465479

DATE FILED: June 5, 1995

PARENT-CASE:

This is a continuation of application Ser. No. 08/083,859, filed Jun. 28, 1993, now abandoned, which is a continuation of application Ser. No. 07/265,061, filed Oct. 31, 1988, now abandoned.

INT-CL: [06] G01N033/549,G01N033/543

US-CL-ISSUED: 436/535, 210/198.3 , 210/500.21 , 210/500.23 , 210/500.41 , 210/638 , 210/656 , 435/6 , 435/180 , 435/181 , 435/182 , 435/287.1 , 435/287.2 , 435/288.1 , 436/161 , 436/178 , 436/518 , 436/531 , 436/532 , 530/413 , 530/417

US-CL-CURRENT: 436/535, 210/198.3 , 210/500.21 , 210/500.23 , 210/500.41

, 210/638 , 210/656 , 435/180 , 435/181 , 435/182 , 435/287.1 , 435/287.2 , 435/288.1 , 435/6 , 436/161 , 436/178 , 436/518 , 436/531 , 436/532 , 530/413 , 530/417

FIELD-OF-SEARCH: 210/198.3; 210/500.21 ; 210/500.23 ; 210/500.41 ; 210/638 ; 210/656 ; 435/180-182 ; 435/6 ; 435/287.1 ; 435/287.2 ; 435/288.1 ; 436/161 ; 436/178 ; 436/518 ; 436/531 ; 436/532 ; 436/535 ; 530/413 ; 530/417

REF-CITED:

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September 1990	Wrasidlo et al.	435/180	N/A	N/A
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ART-UNIT: 182

PRIMARY-EXAMINER: Chin; Christopher L.

ATTY-AGENT-FIRM: Pennie & Edmonds LLP

ABSTRACT:

A method and apparatus for carrying out affinity purification of a ligate. The method comprising, (a) providing a ligate containing liquid to a first side of at least one porous hollow fiber membrane with a ligand immobilized thereto that binds and separates the ligate from the liquid, (b) withdrawing a first portion of the liquid from the first side of the porous hollow fiber membrane, (c) recirculating the first portion of liquid to the first side of the porous hollow fiber membrane, (d) repeating steps (a) to (c) until a majority of the liquid has flowed through the porous hollow fiber membrane, and (e) providing an elution solution to one side of the porous hollow fiber membrane under a pressure sufficient to cause the elution solution to flow into and through the membrane to effect disassociation of any ligate-ligand bonds wherein any ligate bound to the ligand is eluted with the elution solution.

30 Claims, 13 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 12

---------- KWIC ---------

Brief Summary Text - BSTX (7):
2.4 Membrane-Based Affinity

Brief Summary Text - BSTX (47):
Affinity separations, as they are currently practiced, typically involve the following steps: A solution containing the compound of interest is passed through a column containing a highly specific ligand immobilized on a solid . As the fluid passes through the column, the desired component binds selectively--and reversibly--to the ligand; most impurities pass unhindered.

Any residual impurities are removed by flushing the column with an appropriate buffer solution. The compound, now purified but still bound, is then recovered by passing through the column a solution that disrupts the ligand-binding interaction--by changing ionic strength or pH, for instance.

Brief Summary Text - BSTX (48):

Many types of molecules can serve as ligands, including antibodies, antigens, enzyme inhibitors, isolated receptors, and more recently, cloned receptors. Bailon, P., Weber, D. V., Keeney, R. F., Fredericks, J. E., Smith, C., Familletti, P. C., and Smart, J. E. 1987, Receptor-affinity chromatography: a one-step purification for recombinant interleukin-2, Bio/Technology 5:1195. In contrast, however, the choice of materials to the ligand has been limited to either agarose gel beads or silica particles. Although both of these materials are quite suitable for laboratory-scale affinity separations, they do not scale-up well. The intrinsic compressibility of agarose gel beads poses severe limitations for engineering efficient process-scale separation systems. Arnold, F. H., Chalmers, J. J., Saunders, M. S. Croughan, M. S., Blanch, H. W., and Wilke, C. R. 1985; A rational approach to the scale-up of affinity chromatography, pp. 113-122 in Purification of Fermentation Products, D. LeRoith, J. Shiloach, and T. J. Leahy (eds.), American Chemical Society, Washington, D.C.

Brief Summary Text - BSTX (49):

Compressibility may be more than a limitation: it has even been considered a major liability if used in process-scale affinity systems. Clonis, Y. D. 1987, Large-scale affinity chromatography, Bio/Technology 5:1290. The compression and associated tight packing of an agarose gel bed under typical operating conditions can often seriously compromise the throughput of such systems. Silica which have greater structural rigidity, have provided an alternative to agarose gels. Indeed, silica does minimize compression and allows for the high throughputs necessary for a commercial process system. However, high throughputs are realized only at the expense of high operating pressures. And high operating pressures mean increased costs for capital equipment.

Brief Summary Text - BSTX (59):

Mass transfer efficiency is highly dependent upon diffusional path length (L.sub.D). In a packed bed affinity column, this value is necessarily determined by the mean particle radius, hence the trend towards reduced particle size in conventional affinity . Once again, however, there is a trade-off. Improved mass transfer is attained only at the expense of the elevated operating pressures.

Brief Summary Text - BSTX (60):

Membrane-based separation systems, however, largely alleviate the mass transfer limitations seen with conventional technology. Because solute molecules are convected through the membrane past the ligand, rather than having to diffuse to a bead or particle to reach the ligand, diffusional path lengths are minimized and mass transfer efficiency increases significantly. However, even in the case of membranes there is a conflict between high capacity and good mass transfer characteristics which necessitate careful membrane design.

Brief Summary Text - BSTX (65):

2.4 Membrane-Based Affinity

Brief Summary Text - BSTX (72):

Hollow fiber membranes are particularly susceptible to damage during backflushing (and the stresses of star-up/shut-down cycles) because they are self supporting. Flat sheet membranes usually have porous (hydrophobic) backing material to provide mechanical .

Brief Summary Text - BSTX (77):

Stimpson, D. E. ACS Poller Preprints, Vol. 27, No. 2, pg424 (September 1986) studied anisotropic hollow fiber membranes over a wide pore size range as affinity and concluded that pores in the size range of about 0.1 .mu.m are preferred for achieving the best compromise between surface area and pore size.

Detailed Description Text - DETX (45):

The covalent binding of the surface ligand layers need not necessarily involve the intermediacy of a linker moiety although in certain cases, a "linker molecule" is best employed. It is possible, for example, to render certain functional groups of macromolecules already bound to the polymer surface more reactive towards the functional groups of an added ligand by employing activating reagents. These methods which lead to active sites on the macromolecule are well known in the art and include the use of such reagents as dialkylcarbodiimides (for forming amide bonds), diazotization (for coupling aromatic groups), cyanogen bromide (most commonly used for the activation of solid), epoxides, sulfonyl chlorides, or other processes, such as the use of 2-fluoro-1-methylpyridinium p-toluensulfonate (FMP), which facilitate the coupling reaction by introducing a superior leaving group. Other nonlimiting reagents which may be used to covalently bind the ligand to the macromolecule or polymer surface include diepoxides, haloepoxides,

2,4,6-trichloro-S-triazines, diacid chlorides, dialdehydes, diisocyanates, or haloalkylcarboxylic acids.

Detailed Description Text - DETX (60):

Examples of other suitable polymer pairs which may be utilized in this invention include, but are not limited to: polysulfone (PS)/PEO; PES/Polyvinyl pyrrolidone (PVP) (particularly the high molecular weight forms, e.g., MW about 360,000 of PVP); PS/PVP (MW .about.360,000); Polyvinylidene fluoride (/PEO; PES/Epichlorohydrin copolymers of PEO; PES/Polyvinyl alcohol ( ); Polyphenylene oxide (PPO)/Hydrophilized forms of polystyrene (including copolymers and sulfonylated polystyrene); poly(acrylonitrile) (PAN) and copolymers/hydrophilic acrylic polymers (including polyacrylamide), or PVP; PES/hydrophilized forms of PES (including sulfonated PES); and PS/hydrophilized forms of PS.

Detailed Description Text - DETX (66):

In effect this invention has succeeded in harnessing a thermal phase inversion process initiated at a high temperature by an almost instantaneous change in the temperature of the entire dope composition which, in turn, is brought about by immersing the solution in a quenching bath. Not seeking to be limited by theory, it is believed that the resulting microphase separated binary polymer system has a substantially isotropic microstructure as a result of the uniform rapid transfer of heat. The microstructure is then "frozen" and preserved in the integral by a secondary process, occurring simultaneously with the thermal phase inversion, involving the diffusion of the nonsolvent quenching medium. This combination of a high-temperature phase inversion and nonsolvent quench processes provides which are substantially isotropic and which can be made relatively thick and self-supporting. The description substantially isotropic is meant to encompass perfectly isotropic pore size distributions as well as a distribution of pore size within about one order of magnitude as determined by porometry, by passage of latex or by examination using scanning electron microscopy (SEM). Methods for determination of particle size by porometry are documented in the "Operator's Handbook for Coulter Porometer", issue A, June 1986, Part 9903175 (issued by Coulter Electronics Limited, Northwell Dr., Luton, Beds., England).

Detailed Description Text - DETX (67):

While current techniques for preparing microporous hollow fibers are capable of producing with surface pores ranging from tenths of a micron to several microns in diameter, such conventional of the prior art typically retain particles more than an order of magnitude smaller than the surface pore size. As an example, the nominal 0.2 .mu.m-rated hollow fiber

commercially available from AG Technology (Needham, Mass.) has been found to substantially completely reject latex as small as 0.03 .mu.m; which is more than an order of magnitude smaller than the surface pore size of about 1 .mu.m as revealed by SEM examination. Furthermore, SEM examination reveals that pores rapidly decrease in diameter to less than 0.1 .mu.m below the lumen surface over a distance of a few microns. SEM studies of such a after a 0.03 .mu.m latex challenge test shows entrapment of latex particles within the finely porous region in the matrix below the lumen surface.

Detailed Description Text - DETX (68):

A typical microporous hollow fiber of the present invention was determined by SEM to contain surface pores in the range of 1 .mu.m. Latex challenge tests, as a means for defining isotropy, show that latex particles as large as 0.25 .mu.m passed freely across the wall. Furthermore, SEM examination of the hollow fiber wall confirmed that pore size distribution across the entire wall was substantially isotropic, with the smallest pores in the fiber wall typically being no smaller than about 0.3 .mu.m.

Detailed Description Text - DETX (76):

2. This portion consists of a ring with a plurality of spokes radiating to the center where the spokes provide for the hollow bore injection pin--the bore or intraannular fluid for making a hollow fiber passes through one of these spokes to the bore injection pin;

Detailed Description Text - DETX (90):

In extruding preferred PES/PEO dope compositions a number of bore injection (intraannular) fluids can be employed to good effect. These include: water, water/solvent (e.g., NMP) mixtures, pure solvents (e.g., NMP), water soluble polymer solutions (e.g.,), gas (e.g., nitrogen), humidified gas, various non-solvents and liquids which are immiscible with components in the dope, according to one's ultimate goal. When making relatively isotropic microporous membranes with surface pores in the range of 1 .mu.m, the preferred bore injection fluid is a water/NMP mixture.